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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/211,297	12/14/1998	WILLIAM J. BOYLE	A-451-F	7253

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AMGEN INCORPORATED
MAIL STOP 27-4-A
ONE AMGEN CENTER DRIVE
THOUSAND OAKS, CA 91320-1799

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/211,297	BOYLE, WILLIAM J.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *82-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Amendments and/or Claims

The amendment filed has been entered in full. Claims 1-81 were cancelled. Claims 82-92 were added. Claims 82-92 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The objection of claims 64, 69, 75 and 81 under 37 CFR 1.75(c) as being improper multiple dependent claims as set forth at pages 2-3 of the previous Office Action (27 March 2003) is *withdrawn* in view of the amendment (23 September 2003).

The rejection of claims 69 and 81 under 35 U.S.C. 112, first paragraph, written description (new matter) as set forth at pages 2-5 of the previous Office Action (27 March 2003) is *withdrawn* in view of the amendment (23 September 2003).

The rejection of claims 69 and 81 under 35 U.S.C. 112, first paragraph, enablement as set forth at pages 5-6 of the previous Office Action (27 March 2003) is *withdrawn* in view of the amendment (23 September 2003).

The rejection of claims 58, 60, 70, 72 under 35 U.S.C. 102(e) as being anticipated by Anderson *et al.*, US Patent No. 6,419,929 B1 as set forth at pages 6-8 of the previous Office Action (27 March 2003) is *withdrawn* in view of the amendment (23 September 2003).

The rejection of claims 59, 60, 71, 72 under 35 U.S.C. 102(e) as being anticipated by Gorman *et al.*, US Patent No. 6,242,586 B1 as set forth at pages 8-9 of the previous Office Action (27 March 2003) is *withdrawn* in view of the amendment

(23 September 2003).

The rejection of claims 62, 63, 65-68, 73, 74, 77-80 under 35 U.S.C. 103(a) as being unpatentable over Anderson *et al.,* US Patent No. 6,419,929 B1 in view of Gorman *et al.,* as set forth at pages 9-10 of the previous Office Action (27 March 2003) is *withdrawn* in view of the amendment (23 September 2003).

The rejection of claim 76 under 35 U.S.C. 103(a) as being unpatentable over Gorman *et al.*, US Patent No. 6,242,586 B1 in view of Cabilly *et al.*, US Patent No. 4,816,567 as set forth at page 11 of the previous Office Action (27 March 2003) is *withdrawn* in view of the amendment (23 September 2003).

Claim Rejections - 35 USC § 112, first paragraph, enablement

Claims 82-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pages 5-6 of the previous Office Action (27 March 2003).

Applicants argue that in view of the Jakobovits (Curr. Opinion Biotech., 1995) and Bruggemann *et al.* (Immunol. Today, 1996) references cited by the Examiner, teachings were available whereby one skilled in the art could construct a transgenic mouse capable of producing human antibodies. Those teachings could be used to make other transgenic animals capable of producing human antibodies. Citing the Jakobovits

and Bruggerman references, the Examiner argues that making transgenic animals which are capable of producing heterologous antibodies is extremely complex and unpredictable. Applicants maintain that there is no evidence that one could not use the teachings in the art to make a transgenic animal other than a transgenic mouse for producing human antibodies. Applicants state that the Jakobovits and Bruggeman references teach that many crucial steps, such as the inactivation of the host Ig genes and expression of human Ig genes upon transfer to the new host, have now been accomplished. Applicants maintain that the art enables the making of transgenic animals capable of producing human antibodies without undue experimentation.

Applicants' arguments have been fully considered but not deemed persuasive. The conclusion for lack of enablement was reached by weighing all of the Wands Factors. If one skilled in the art can readily anticipate the effect, than there is predictability in the art. In this case, however, the art is unpredictable and extremely complex. The evidence for the degree of predictability in the art also relates to the amount of direction needed in the specification. The specification as originally filed is not enabled because it fails to provide sufficient guidance regarding expressing human antibodies directed against osteoprotegerin binding protein in transgenic non-human animals.

The references cited by the Examiner teach the drawbacks regarding human antibody production in mice. Contrary to Applicants' assertion, the references fail to establish the ease of producing antigen-specific human antibodies. Jakobovits states that human Ig transgenic mice are capable of mounting an antigen-specific human

antibody response upon immunization with model antigens, such as tetanus toxic C and human antigens such as CD4 and IgE. The reference does not address antibodies made against various protein sequences or fragments. Jakobovits also stresses the importance of *fully* inactivating mouse Ig genes to greatly increase human antibody production in mice (antibody titer). Bruggemann *et al.* state that in contrast to most *in vitro* procedures, the *in vivo* isolation of B cells expressing antigen-specific antibodies does not appear to occur by a single stage of diversification followed by a stage of antigene selection. Rather, the diversification occurs in two distinct phases. Bruggemann *et al.* state that the major issue is whether human Ig transloci introduced into the mouse germline can elicit specific antibodies of very high affinity. Bruggemann *et al.* state that to date, transgenesis has been achieved using miniloci, yeast artificial chromosomes and bacteriophage P1 vectors and discuss the drawbacks with each gene. The authors teach that a limitation to many of the experiments to date is that *only portions* of the human Ig loci have been transferred into mouse germlines. Furthermore, the instant claims encompass all transgenic non-human animals. The specification, references of record and those cited by the Examiner fail to teach human antibody production in other non-human animals.

The specification lacks working examples, which is not necessary if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Lacking working examples, however is a factor to be considered, especially in a case involving an unpredictable and/or undeveloped art. A considerable amount of time is permissible for the quantity of

experimentation needed to make and/or use the invention based on the disclosure. However this depends on if the invention is routine or if the skilled artisan is given sufficient direction or guidance. In the instant case, the experimentation is not routine and Applicants have failed to provide *any guidance*. Undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
February 9, 2004

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600